REMARKS

Claim Status

Claims 48-62 are pending in the application. Claims 48, 52, 54, 56, 58, and 59 have been amended, and claims 49, 53, 55, 57, and 60 have been canceled without prejudice to Applicants' right to pursue the subject matters in a future application.

Claim Objection

Claim 55 was objected to for having incorrect syntax. The objection is moot because claim 55 has been canceled without prejudice.

Rejection Under 35 U.S.C. §101

Claim 57 was rejected under 35 U.S.C. §101 for reciting a use without setting forth any step. The rejection is moot because claim 57 has been canceled without prejudice.

Rejection Under 35 U.S.C. §112, Second Paragraph

1. Claims 56-59 were rejected under 35 U.S.C. §112, second paragraph, as being indefinite regarding the phrase "super-compound interferon". The rejection is respectfully traversed.

To avoid confusion or being vague, claims 56, 58 and 59 have been amended to delete the phrase "super-compound interferon". Claim 57 has been canceled without prejudice. Accordingly, Applicants respectfully request that the rejection of claims 56, 58 and 59 under 35 U.S.C. §112, second paragraph, be withdrawn.

2. Claims 48-62 were rejected under 35 U.S.C. §112, second paragraph, as being indefinite regarding the phrase "changed

spatial configuration and enhanced biological activity". The rejection is respectfully traversed.

Claims 48 and 52 have been amended to delete the phrase "changed spatial configuration and enhanced biological activity". Accordingly, Applicants respectfully request that the rejection of claims 48-62 under 35 U.S.C. §112, second paragraph, be withdrawn.

3. Claims 53-54 were rejected under 35 U.S.C. §112, second paragraph, as being indefinite regarding the phrase "special promoter". The rejection is moot because claim 53 has been canceled without prejudice.

4. Claims 57-59 were rejected under 35 U.S.C. §112, second paragraph, for reciting "the super-compound interferon". As indicted above, claim 57 has been canceled without prejudice and claims 58 and 59 have been amended to obviate the rejection. Accordingly, Applicants respectfully request that the rejection of claims 58 and 59 under 35 U.S.C. §112, second paragraph, be withdrawn.

5. Claim 57 was rejected under 35 U.S.C. §112, second paragraph, as being indefinite. This rejection is moot because claim 57 has been canceled without prejudice.

Rejection Under 35 U.S.C. §112, 1st Paragraph, Written Description

Claims 48-62 were rejected under 35 U.S.C. §112, 1st paragraph, for failing to comply with the written description requirement.

The Examiner indicates that this is a new matter rejection. The Examiner contends that while the specification does teach a recombinant interferon that is different from INFERGEN as determined by circular dichroism, the specification does not specifically recite a recombinant interferon encoded by SEQ ID NO.1 and having the amino acid sequence of SEQ ID NO.2, and further having enhanced biological activity as compared to an interferon not encoded by SEQ ID NO.1. The rejection is respectfully traversed.

Claims 48 and 52 have been amended to recite a recombinant interferon encoded by a polynucleotide having a sequence of SEQ ID NO.1, wherein the recombinant interferon has an amino acid sequence of SEQ ID NO.2, and the recombinant interferon can directly inhibit secretion of HBsAg and HBeAg of Hepatitis B Virus. Applicants submit that the claimed interferon has been described in the specification in such a way as to reasonably convey to one skilled in the art that the inventor had possession of the claimed subject matter at the time the application was filed.

Example 1 of the present specification discloses a recombinant interferon (rSIFN-co) encoded by a cDNA designed according to the codon usage of *E. coli*. The nucleotide and amino acid sequences for the interferon of the present invention (rSIFN-co) were disclosed in Figure 1 (*see* page 14, lines 10-14). The description for Figure 1 has been amended as follows in an amendment filed April 12, 2006:

Figure 1. rSIFN-co cDNA sequence (SEQ ID NO:1) designed according to *E. Coli.* codon usage and deduced rSIFN-co amino acid sequence (SEQ ID NO:2)

Example 1 of the present specification describes in detail the construction of a cDNA encoding the interferon of the present invention, rSIFN-co (*see* pages 14-19). Then the nucleotide and amino acid sequences for rSIFN-co were listed on pages 20-21. The heading for such sequences on page 20 has been amended as follows in an amendment filed April 12, 2006:

> rSIFN-co CDNA SEQUENCE (SEQ ID NO:1) DESIGNED ACCORDING TO E. COLI. CODON USAGE AND DEDUCED rSIFN-co AMINO ACID SEQUENCE (SEQ ID NO:2)

Example 2 of the present specification describes method of purifying the interferon of the present invention (rSIFN-co). Example 3 describes the stability of lyophilized rSIFN-co. Example 4 discloses inhibition of HBV viral antigen secretion by rSIFN-co, the interferon of the present invention (*see* page 32, lines 5-17; Tables 1-3). Hence, taking the present disclosure as a whole, one of ordinary skill in the art would readily and reasonably conclude that at the time the application was filed the inventor had possession of a novel interferon having a sequence of SEQ ID NO.2 which is encoded by SEQ ID NO.1, and such novel interferon can directly inhibit secretion of HBsAg and HBeAg of Hepatitis B Virus. Accordingly, no new matter has been added by the present amendment, and Applicants respectfully request that the rejection of claims 48-62 under 35 U.S.C. §112, 1st paragraph, be withdrawn.

Rejection Under 35 U.S.C. §112, 1st Paragraph, Enablement

Claims 52-62 were rejected under 35 U.S.C. §112, 1st paragraph, for lack of enablement. Claim 52 was rejected for reciting "a host cell", and claims 53-62 were rejected for depending from claim 52.

Applicants submit that claim 52 has been amended as helpfully suggested by the Examiner to recite "an isolated host cell". Accordingly, Applicants respectfully request that the rejection of claims 52-62 under 35 U.S.C. §112, 1st paragraph, be withdrawn.

Rejection Under 35 U.S.C. §102(b)

1. Claims 48, 49, 52, 53, and 55-60 were rejected under 35 U.S.C. 102(b) as being anticipated by Stabinsky (U.S. Patent 4,695,623 or U.S. Patent 4,897,471) or Alton et al. (EP 422697). The rejection is respectfully traversed.

The Examiner contends that because a recombinant interferon having a sequence of SEQ ID NO.2 is what is actually being claimed, the disclosure of the above cited references, which all teach a polypeptide having the sequence of SEQ ID NO.2, meet the limitations of claim 48. The Examiner further argues that although the '623 patent does not specifically recite an interferon capable of directly inhibiting DNA duplication and secretion of HBsAg and HBeAg of the hepatitis B virus, the interferon of the '623 patent would inherently possess such inhibitory activities on hepatitis B virus. Applicants respectfully disagree.

Contrary to the Examiner's assertion, Applicants submit that the interferon of the above cited references does not inherently possess the ability to inhibit secretion of HBsAg and HBeAg of the hepatitis B virus. The '623 patent, '471 patent and the '697 application all have the same specification and are all owned by Amgen Inc. These three publications disclose a consensus interferon having an amino acid sequence of SEQ ID NO.2, but the consensus interferon is not encoded by nucleotide sequence SEQ ID NO.1 (*see e.g.* Example 9 and Table VIII of the '623 patent). Amgen Inc. later marketed this consensus interferon as INFERGEN (*see* **Exhibit 1**, the product sheet of Amgen's INFERGEN).

The present specification clearly shows Amgen's INFERGEN cannot inhibit secretion of HBV HBsAg and HBeAg (*see* page 32, lines 5-17; Tables 1-3). As shown in Table 3, Amgen's INFERGEN does not show any dose-dependent inhibition on the secretion of HBV HBsAg and HBeAg, whereas the interferon of the present invention exhibits highly significant dose-dependent inhibition on the secretion of HBV HBsAg and HBeAg (*see* Table 1).

In conclusion, neither one of '623 patent, '471 patent and the '697 application anticipates the claimed interferon of the present invention because none of the cited references teaches an interferon that can inhibit secretion of HBV HBsAg and HBeAg. Furthermore, none of the cited references teaches an interferon encoded by nucleotide sequence SEQ ID NO.1. Claims 49, 53, 55, 57, and 60 have been canceled without prejudice. Accordingly, Applicants respectfully request that the rejection of claims 48, 52, 56, 58 and 59 under 35 U.S.C. 102(b) be withdrawn.

2. Claims 48-51 were rejected under 35 U.S.C. 102(b) as being anticipated by Blatt et al. (U.S. Patent 5,372,808). The Examiner rejects the claims on the same basis as described for the above 102 rejection. This rejection is respectfully traversed.

The '808 patent, a patent owned by Amgen Inc., describes the use of a consensus interferon IFN-con_1, which is the same as INFERGEN as described in the three references cited in the above 102 rejection (*see* column 9, lines 5-10). As discussed above, Applicants reiterate that consensus interferon IFN-con_1 (or INFERGEN) does not inhibit secretion of HBV HBsAg and HBeAg as claimed herein.

Hence, Blatt et al. neither teach or suggest a recombinant interferon encoded by a polynucleotide having a sequence of SEQ ID NO:1, nor Blatt et al. teach or suggest a recombinant interferon capable of inhibiting secretion of HBV HBsAg and HBeAg. Accordingly, Blatt et al. do not anticipate claim 48 of the instant application, and Applicants respectfully request that the rejection of claims 48-51 under 35 U.S.C. 102(b) be withdrawn.

Rejection Under § 103(a)

Claims 48-62 were rejected under 35 U.S.C. 103(a) as being unpatentable over Stabinsky (U.S. Patent 4,695,623) or Stabinsky (U.S. Patent 4,897,471) or Alton et al. (EP 422697) in view of Nasoff et al. (1999). The rejection is respectfully traversed.

The primary references of the '623 patent, '471 patent and the '697 application have been discussed above. The Examiner cites Nasoff et al. for teaching on pBAD promoter.

As discussed above, the three primary references do not teach or suggest an interferon that can inhibit viral antigen secretion of hepatitis B virus. Hence, for the sake of argument, even though assuming it is appropriate to combine the cited references (a point Applicants do not concede), the Examiner has not established a *prima facie* case of obviousness because the combined teaching of the cited references does not teach or suggest all the claim limitations. *see* MPEP 2143. Thus, claims 48 and 52 are not obvious in view of the cited references. In view of the above remarks, Applicants respectfully request that the rejection of claims 48-62 under 35 U.S.C. 103(a) be withdrawn.

Double Patenting

Claims 48-62 were provisionally rejected on the ground of non-statutory obviousness-type double patenting as being unpatentable over claims 1-13 of copending Application No. 10/928,956.

Claims 48-62 were also provisionally rejected on the ground of non-statutory obviousness-type double patenting as being unpatentable over claims 1, 5, 12-17 and 21 of copending Application No. 11/077,813.

The Examiner indicates that this is a provisional rejection because the conflicting claims have not been allowed. Accordingly, Applicants respectfully request that the provisional

double patenting rejection be held in abeyance until there are allowable claims.

CONCLUSION

Applicants respectfully maintain that all the grounds of rejections raised in the March 7, 2007 Final Office Action have been addressed and earnestly urge the Examiner to render favorable action for the claimed invention.

If a telephone interview would be of assistance in advancing the prosecution of the subject application, Applicant's undersigned attorney invites the Examiner to telephone him at the number provided below. If any additional fee is required, authorization is hereby given to charge the amount of any such fee to Deposit Account No. 50-1891.

Respectfully submitted,

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EXHIBIT 1

AMGEN

Infergen®
(Interferon alfacon-1)

DESCRIPTION

Interferon alfacon-1 is a recombinant non-naturally occurring type-I interferon. The 166-amino acid sequence of interferon alfacon-1 was derived by scanning the sequences of several natural interferon alpha subtypes and assigning the most frequently observed amino acid in each corresponding position.[1] Four additional amino acid changes were made to facilitate the molecular construction, and a corresponding synthetic DNA sequence was constructed using chemical synthesis methodology. Interferon alfacon-1 differs from interferon alfa-2 at 20/166 amino acids (88% homology), and comparison with interferon-beta shows identity at over 30% of the amino acid positions. Interferon alfacon-1 is produced in *Escherichia coli (E coli)* cells that have been genetically altered by insertion of a synthetically constructed sequence that codes for interferon alfacon-1. Prior to final purification, Interferon alfacon-1 is allowed to oxidize to its native state, and its final purity is achieved by sequential passage over a series of chromatography columns. This protein has a molecular weight of 19,434 daltons. Infergen® is the Amgen Inc. trademark for Interferon alfacon-1.

Infergen is a sterile, clear, colorless, preservative-free liquid formulated with 100 mM sodium chloride and 25 mM sodium phosphate at pH 7.0 ± 0.2. The product is available in single-use vials and prefilled syringes containing 9 mcg and 15 mcg interferon alfacon-1 at a fill volume of 0.3 mL and 0.5 mL, respectively. Infergen vials and prefilled syringes contain 0.05 mg/mL of interferon alfacon-1, 5.9 mg/mL sodium chloride, and 3.8 mg/mL sodium phosphate in Water for Injection, USP. The Infergen Singleject™ prefilled syringe has a glass barrel and a 26 gauge, 5/8 inch needle. Infergen is to be administered undiluted by subcutaneous (SC) injection.

- Formulation, filling and packaging operations for Infergen are performed by Amgen Puerto Rico, a wholly-owned subsidiary of Amgen Inc.

CLINICAL PHARMACOLOGY

General

Interferons are a family of naturally occurring, small protein molecules with molecular weights of 15,000 to 21,000 daltons that are produced and secreted by cells in response to viral infections or to various synthetic and biological inducers. Two major classes of interferons have been identified (ie, type-I and type-II). Type-I interferons include a family of more than 25 interferon alphas as well as interferon beta and interferon omega. While all alpha interferons have similar biological effects, not all the activities are shared by each alpha interferon and, in many cases, the extent of activity varies substantially for each interferon subtype.

All type-I interferons share common biological activities generated by binding of interferon to the cell-surface receptor, leading to the production of several interferon-stimulated gene products. Type-I interferons induce pleiotropic biologic responses which include antiviral, antiproliferative and immunomodulatory effects, regulation of cell surface major histocompatibility antigen (HLA class I and class II) expression and regulation of cytokine expression. Examples of interferon-stimulated gene products include 2′5′ oligoadenylate synthetase (2′5′ OAS) and β-2 microglobulin.

The antiviral, antiproliferative, NK cell activation, and gene-induction activities of Infergen have been compared with other recombinant alfa interferons in *in vitro* assays and have demonstrated similar ranges of activity. Infergen exhibited at least five times higher specific activity *in vitro* than Interferon alfa-2a and Interferon alfa-2b.[2] Comparison of

Infergen with a WHO international potency standard for recombinant interferon alfa (63/54) revealed that the specific activity of Infergen in both an *in vitro* antiviral cytopathic effect assay and an antiproliferative assay was 1 x 10^8 U/mg. However, correlation between *in vitro* activity and clinical activity of any interferon is unknown.

Pharmacokinetics and Pharmacodynamics

The pharmacokinetic properties of Infergen have not been evaluated in patients with chronic hepatitis C. Pharmacokinetic profiles were evaluated in normal, healthy volunteer subjects after SC injection of 1, 3, or 9 mcg Interferon alfacon-1. Plasma levels of Infergen after SC administration of any dose were too low to be detected by either ELISA or by inhibition of viral cytopathic effect. However, analysis of Infergen-induced cellular products (induction of 2′5′ OAS and β-2 microglobulin) after treatment in these subjects revealed a statistically significant, dose-related increase in the area under the curve (AUC) for the levels of 2′5′ OAS or β-2 microglobulin induced over time ($p < 0.001$ for all comparisons). Concentrations of 2′5′ OAS were maximal at 24 hours after dosing, while serum levels of β-2 microglobulin appeared to reach a maximum at 24 to 36 hours after dosing. The dose-response relationships observed for 2′5′ OAS and β-2 microglobulin were indicative of biological activity after SC administration of 1 to 9 mcg Infergen.

Preclinical Experience

All interferons have been shown to be highly species specific. Antiviral activity of Infergen was observed in the rhesus monkey LLC cell line and golden Syrian hamster BHK cell line. Antiviral activity of Infergen in the golden Syrian hamster was confirmed further *in vivo*.[3] Pharmacokinetic studies of Infergen in golden Syrian hamsters and rhesus monkeys demonstrated rapid absorption following SC injection. Peak serum concentrations of Infergen were observed at 1 hour and 4 hours in golden Syrian hamsters and in rhesus monkeys, respectively. Subcutaneous bioavailability was high in both species, averaging 99% in golden Syrian hamsters and 83% to 104% in rhesus monkeys. Clearance of Infergen, averaging 1.99 mL/minute/kg in golden Syrian hamsters and 0.71 to 0.92 mL/minute/kg in rhesus monkeys, was due predominantly to catabolism and excretion by the kidneys. The terminal half-life of Infergen following SC dosing was 1.5 hours in golden Syrian hamsters and 3-4 hours in rhesus monkeys. Upon 7-day multiple SC dosing, no accumulation of serum levels was observed in golden Syrian hamsters.

In preclinical toxicology studies in golden Syrian hamsters and rhesus monkeys, administration of Infergen at doses of up to 100 mcg/kg/day was associated with decreased body weight, decreased food consumption, and bone marrow suppression. High-dose chronic exposure at doses of 10 to 100 mcg/kg/day (50- to 500-fold higher than the maximum clinical dose given daily) in rhesus monkeys was not tolerated for greater than 1 month due to the development of vascular leak syndrome.

Reproductive toxicity studies in pregnant rhesus monkeys and golden Syrian hamsters demonstrated an increase in fetal loss in hamsters treated with Infergen at doses of greater than 150 mcg/kg/day, and in rhesus monkeys at doses of 3 and 10 mcg/kg/day. The Infergen toxicity profile described is consistent with the known toxicity profile of other alfa interferons.[4]

CLINICAL EXPERIENCE: RESPONSE TO INFERGEN

Infergen was studied in an open-label dose escalation study using 3, 6, 9, 12, or 15 mcg administered three times per week (TIW) to patients with compensated liver disease secondary to chronic hepatitis C virus (HCV) infection. The 15 mcg dose was the maximal tolerated dose. All doses demonstrated an acceptable safety profile and preliminary evidence of efficacy.

The efficacy of 3 and 9 mcg doses of Infergen in the treatment of chronic HCV infection was examined in a randomized, double-blind clinical trial involving 704 patients previously untreated with alfa interferon. Patients were 18 years or older, had compensated liver disease, tested positive for HCV RNA, and had elevated serum alanine aminotransferase (ALT) concentrations averaging > 1.5 times the upper limit of normal. Staging of chronic liver disease was confirmed by a liver biopsy taken within 1 year prior to enrollment. Other causes of chronic liver disease were ruled out prior to randomization. Notable exclusion criteria were decompensated liver disease, thyroid abnormality, or history of depression.

Efficacy of Infergen therapy was assessed on an intent to treat basis and was determined by measurement of serum ALT concentrations at the end of therapy (24 weeks) and following 24 weeks of observation after the end of treatment. Serum HCV RNA was also assessed using a quantitative reverse transcriptase polymerase chain reaction (RT-PCR) assay with a lower limit of sensitivity of 100 copies/mL. Liver histology was assessed by comparing the histology activity index (HAI) score[a] of a pretreatment biopsy specimen with the HAI score from a specimen obtained 24 weeks after cessation of interferon therapy.

Patients enrolled in the study were randomized to one of three treatment groups: Infergen at a dose of 9 mcg (n = 257), Infergen at a dose of 9 mcg (n = 232), or Interferon alfa-2b recombinant [IFN α-2b, Intron® A (Interon® is a registered trademark of the Schering Corporation)] at a dose of 3 million international units (IU) (approximately 15 mcg) (n = 240). All patients were scheduled to receive their respective interferons SC TIW for 24 weeks (end of treatment). Following treatment, patients were observed for an additional 24 weeks to assess durability of ALT normalization (end of post-treatment observation). In all patients, a complete response was defined as a decrease in serum ALT concentration to at or below the upper limit of normal (48 U/L) at the end of the post-treatment observation period, even if ALT normalization had not been observed at the end of treatment. Complete response was dependent on two consecutive normal serum ALT values determined 4 weeks apart. Reduction of HCV RNA to < 100 copies/mL was measured as a secondary efficacy endpoint (two consecutive measurements).

Sustained response rates by ALT normalization and HCV RNA reductions to below detectable limits are included in Table 1. Among the Infergen treatment groups in this study, the 9 mcg dosage arm demonstrated a similar efficacy profile when compared to the IFN α-2b dosage arm. The 3 mcg Infergen dosage arm had lesser efficacy; 3% of patients receiving 3 mcg Infergen had sustained reductions in their ALT concentrations to within the normal range and 3% had sustained reductions in HCV RNA to below detectable limits.

Table 1. Rates (95% CI[a]) of ALT Normalization and HCV RNA Reductions to Below Detectable Limits

	End of 24-week Treatment		End of Observation (Sustained Response Rate)	
	Infergen 9 mcg	IFN α-2b 3 Million IU[b]	Infergen 9 mcg	IFN α-2b 3 Million IU[b]
Normalized ALT	39% (33%, 46%)	35% (29%, 41%)	17% (12%, 22%)	17% (13%, 22%)
HCV RNA Negative	33% (27%, 39%)	25% (19%, 31%)	9% (6%, 14%)	8% (5%, 13%)

[a] CI = Confidence Interval.

[b] 3 million IU IFN α-2b is equivalent to approximately 15 mcg IFN α-2b.

In this study, liver biopsies were taken at baseline and at the end of post-treatment observation. Similar improvement in liver histology, assessed by HAI score,[a] was observed in the 9 mcg Infergen (68%), 3 mcg Infergen (63%), and IFN α-2b (65%) dosage arms.

Subsequent treatment with 15 mcg of Infergen was evaluated in an open-label clinical trial in 107 patients who had failed initial therapy with either 9 mcg Infergen or 3 million IU (approximately 15 mcg) IFN α-2b. Of these patients, 74/107 had failed to normalize ALT concentrations during either the initial treatment period or the post-treatment observation period, while 33/107 achieved a normal ALT concentration during initial treatment, but experienced relapse (return of abnormal ALT concentration) during post-treatment observation. Patients were assessed for normalization of ALT (ALT response rate) and HCV RNA reduction to < 100 copies/mL (HCV response rate) at the end of 24 weeks of observation. Response rates (expressed as fraction of patients, percentage of patients, and 95% confidence interval of percentage) are presented for all patients and two subsets of patients: patients who had relapsed following initial therapy and patients who had never normalized following initial therapy.

Overall 16/107 [15% (9-23% CI)] patients had a sustained ALT response. Of patients who had relapsed following initial therapy 10/53 [30% (16-69% CI)] had a sustained ALT response and 6/74 [8% (3-17% CI)] who never normalized their ALT concentration had a sustained ALT response. Overall 10/107 [9% (5-17% CI)] patients had a sustained HCV response

(< 100 copies/mL). Of patients who had relapsed following initial therapy 8/32 [25% (11-43% CI)] had a sustained HCV response and 2/75 [3% (0-9% CI)] who never had a reduction in HCV RNA to < 100 copies/mL had a sustained HCV response.

Serum antibody levels were measured in all patients using both an Infergen-binding radioimmunoassay and an IFN α-2b-binding ELISA. A patient was considered to have developed binding antibodies if, using serum samples from two consecutive time points, a positive response was detected in either assay. The number of patients developing positive binding antibody responses in either assay was similar in the 9 mcg Infergen (11%) and 3 million IU IFN α-2b groups (15%). The titer of neutralizing antibodies to interferon was not measured. Sustained ALT response rates in patients treated with Infergen who developed binding antibodies (4/25) were similar to sustained ALT response rates in patients who did not develop detectable antibody titers (40/195). The most frequently observed time to first antibody response was week 16 of interferon treatment. Following cessation of interferon therapy, the number of patients with a positive antibody response declined during post-treatment observation.

INDICATIONS AND USAGE

Infergen is indicated for the treatment of chronic HCV infection in patients 18 years of age or older with compensated liver disease who have anti-HCV serum antibodies and/or the presence of HCV RNA. Other causes of hepatitis, such as viral hepatitis B or autoimmune hepatitis should be ruled out prior to initiation of therapy with Infergen. In some patients with chronic HCV infection, Infergen normalizes serum ALT concentrations, reduces serum HCV RNA concentrations to undetectable quantities (< 100 copies/mL), and improves liver histology.

CONTRAINDICATIONS

Infergen is contraindicated in patients with known hypersensitivity to alpha interferons, to *E coli*-derived products, or to any component of the product.

WARNINGS

Treatment with Infergen should be administered under the guidance of a qualified physician, and may lead to moderate-to-severe adverse experiences requiring dose reduction, temporary dose cessation, or discontinuation of further therapy.

Withdrawal from study for adverse events occurred in 7% of patients treated with 9 mcg Infergen (including 4% due to psychiatric events).

SEVERE PSYCHIATRIC ADVERSE EVENTS MAY MANIFEST IN PATIENTS RECEIVING THERAPY WITH INTERFERON, INCLUDING INFERGEN. DEPRESSION, SUICIDAL IDEATION, AND SUICIDE ATTEMPT MAY OCCUR. The incidence of psychiatric events of suicidal ideation was small (1%) for patients treated with 9 mcg Infergen compared to the overall incidence (5%) of psychiatric events. Infergen should be used with caution in patients who report a history of depression and physicians should monitor all patients for evidence of depression. Physicians should inform patients of the possible development of depression prior to initiation of Infergen therapy, and patients should report any sign or symptom of depression immediately. Other prominent psychiatric adverse events may also occur, including nervousness, anxiety, emotional lability, abnormal thinking, agitation, or apathy (see PRECAUTIONS).

INFERGEN SHOULD BE ADMINISTERED WITH CAUTION TO PATIENTS WITH PRE-EXISTING CARDIAC DISEASE. Hypertension and supraventricular arrhythmias, chest pain and myocardial infarction have been associated with interferon therapies.[a]

No studies with Infergen have been conducted in patients with decompensated hepatic disease. Patients with decompensated hepatic disease should not be treated with Infergen, and patients who develop symptoms of hepatic decompensation, such as jaundice, ascites, coagulopathy, or decreased serum albumin, should halt further interferon therapy.

PRECAUTIONS

General

Since the use of type-I interferons has been associated with depression, Infergen therapy should not be used in patients with a history of severe psychiatric disorders and should be discontinued in patients developing severe depression, suicidal ideation, or other severe psychiatric disorders (see WARNINGS).

Infergen should be used with caution in patients with a history of cardiac disease. Hypotension (5%), tachycardia (4%), and palpitation (3%) were the most common cardiovascular adverse events reported for 9 mcg Infergen therapy, with 1% of patients reporting tachyarrhythmias which were dose-limiting (see WARNINGS).

Infergen should be used cautiously in patients with abnormally low peripheral blood cell counts or who are receiving agents that are known to cause myelosuppression. Leukopenia, particularly granulocytopenia, may be severe in patients treated with alpha interferons, including Infergen, and may necessitate dose reduction or temporary dose cessation. Thrombocytopenia is a common, but less severe, event often associated with alpha interferon therapy. Therapy should be withheld if the absolute neutrophil count (ANC) is < 500 x 10^9/L or if the platelet count is < 50 x 10^9/L. Transplantation patients, or other clinically immunosuppressed patients, should receive Infergen therapy with caution.

Serious acute hypersensitivity reactions have been reported in rare instances following treatment with alpha interferons. If hypersensitivity reactions occur (eg, urticaria, angioedema, bronchoconstriction, anaphylaxis), the drug should be discontinued immediately and appropriate medical treatment instituted.

Infergen should be administered with caution to patients with a history of endocrine disorders. Abnormal thyroid stimulating hormone (TSH) and free thyroxine (T_4) level with hypothyroidism occurred in 4% of patients administered 9 mcg Infergen, and thyroid supplements were required in approximately two thirds of those patients.

Ophthalmologic disorders have been reported with treatment with alpha interferons. Investigators using alpha interferons have reported the occurrence of retinal hemorrhages, cotton wool spots, and retinal artery or vein obstruction in rare instances. Any patient complaining of loss of visual acuity or visual field should have an eye examination. Because these ocular events may occur in conjunction with other disease states, a visual exam prior to initiation of interferon therapy is recommended in patients with diabetes mellitus or hypertension.

Exacerbation of autoimmune disease has been reported in patients receiving type-I interferon therapy. Infergen should not be used in patients with autoimmune hepatitis and be used with caution in patients with other autoimmune disorders.

While fever may be related to the flu-like symptoms reported in patients treated with Infergen, when fever occurs, other possible causes of persistent fever should be ruled out.

Information for Patients

If home use is determined to be desirable by the physician, instructions on appropriate use should be given by a health care professional. The patient must be instructed as to the proper dosage and administration. Information included in the full "Information for Patients" leaflet (provided separately) should be fully reviewed with the patient; it is not a disclosure of all, or possible, adverse effects. The most common adverse reactions occurring with Infergen therapy are flu-like symptoms including fatigue, fever, rigors, headache, arthralgia, myalgia, and increased sweating. Non-narcotic analgesics and bedtime administration of Infergen may be used to prevent or lessen some of these symptoms. Additionally, patients must be thoroughly instructed in the importance of proper disposal procedures and cautioned against the reuse of needles, syringes, or re-entry of the drug product. A puncture-resistant container for the disposal of used syringes and needles should be used by the patient and should be disposed of according to the directions provided by the health care provider.

Laboratory Tests

Laboratory tests are recommended for all patients on Infergen therapy, prior to beginning treatment (baseline), 2 weeks after initiation of therapy, and periodically thereafter during the 24 weeks of therapy at the discretion of the physician. Following completion of Infergen therapy, any abnormal test values should be monitored periodically. The entrance criteria that were used for the clinical study of Infergen may be considered as a guideline to acceptable baseline values for initiation of treatment:

- Platelet count ≥ 75 x 10^9/L
- Hemoglobin concentration ≥ 100 g/L
- ANC ≥ 1500 x 10^9/L
- Serum creatinine concentration < 180 µmol/L (< 2.0 mg/dL) or creatinine clearance > 0.83 mL/second (> 50 mL/minute)
- Serum albumin concentration ≥ 25 g/L
- Bilirubin within normal limits
- TSH and T_4 within normal limits

Neutropenia, thrombocytopenia, hypertriglyceridemia, and thyroid disorders have been reported with administration of Infergen (see ADVERSE REACTIONS). Therefore, these laboratory parameters should be monitored closely.

Drug Interactions

No formal drug interaction studies have been conducted with Infergen. Infergen should be used cautiously in patients who are receiving agents that are known to cause myelosuppression or with agents known to be metabolized via the cytochrome P-450 pathway.[1] Patients taking drugs that are metabolized by this pathway should be examined closely for changes in the therapeutic and/or toxic levels of concomitant drugs.

Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenesis: No carcinogenicity data for Infergen are available in animals or humans.

Mutagenesis: Infergen was not mutagenic when tested in several *in vitro* assays, including the Ames bacterial mutagenicity assay and an *in vitro* cytogenetic assay in human lymphocytes, either in the presence or absence of metabolic activation.

Impairment of Fertility: Infergen at doses as high as 100 mcg/kg did not selectively affect reproductive performance or the development of the offspring when administered SC to male and female golden Syrian hamsters for 70 and 14 days before mating, respectively, and then through mating and to day 7 of pregnancy.

Pregnancy Category C

Infergen has been shown to have embryolethal or abortifacient effects in golden Syrian hamsters when given at 135 times the human dose and in cynomolgus and rhesus monkeys when given at 9 to 81 times (based on body surface area) the human dose. There are no adequate and well-controlled studies in pregnant women. Infergen should not be used during pregnancy. If a woman becomes pregnant or plans to become pregnant while taking Infergen, she should be informed of the potential hazards to the fetus. Males and females treated with Infergen should be advised to use effective contraception.

Nursing Mothers

It is not known whether Infergen is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised if Infergen is administered to a nursing woman. The effect on the nursing neonate of orally ingested Infergen in breast milk has not been evaluated.

Pediatric Use

The safety and effectiveness of Infergen have not been established in patients below the age of 18 years. Infergen therapy is not recommended in pediatric patients.

ADVERSE REACTIONS

Adverse experiences that were reported, regardless of attribution to treatment, in at least 5% of the patients in the 9 mcg Infergen or 3 million IU IFN α-2b groups of the pivotal study are presented in Table 2, listed in decreasing order by the 9 mcg Infergen group. The incidence of adverse events is expressed based on the number of patients experiencing each event at least once during treatment or post-treatment of the study.

Most adverse events were mild-to-moderate in severity and abated with cessation of therapy. Flu-like symptoms (ie, headache, fatigue, fever, rigors, myalgia, sweating increased, and asthralgia) were the most frequently reported treatment-related adverse reactions. Most were short-lived and could be treated symptomatically.

Depression, usually mild-to-moderate in severity, was reported in 26% of patients who received 9 mcg Infergen and was the most common adverse event resulting in study drug discontinuation.

In patients who had tolerated previous interferon therapy and failed to normalize ALT concentration or who had achieved normalization of ALT concentration during the treatment period but who relapsed during the post-treatment observation period, further treatment with 15 mcg TIW of Infergen for 24 weeks was generally tolerated (see Table 2). The higher dose of Infergen used in these patients was associated with a greater incidence of leukopenia and granulocytopenia, and one or more dose reductions for all causes were required in 33% of patients. Patients who do not tolerate initial standard interferon therapy should not receive therapy with 15 mcg TIW of Infergen.

Table 2. Patient Incidence of Adverse Events in Phase 3 Clinical Trials Regardless of Attribution*

		Initial Treatment†		Subsequent Treatment‡
		Infergen 9 mcg (n = 231)	IFN α-2b 3 Million IU (n = 236)	Infergen 15 mcg (n = 165)
Body System	Preferred Term	Percentage of Patients		Percentage of Patients
APPLICATION SITE	Injection Site Erythema	23	15	17
	Injection Site Pain	9	3	8
	Injection Site Ecchymosis	6	7	5
BODY AS A WHOLE	Body Pain	54	45	39
	Influenza-like Symptoms§	15	11	8
	Hot Flashes	13	7	7
	Pain Chest - Non-cardiac	13	14	5
	Malaise	11	10	2
	Asthenia	9	11	10
	Edema Peripheral	9	8	4
	Access Pain	8	9	1
	Allergic Reaction	7	5	3
	Weight Decrease	5	7	5
CARDIO-VASCULAR	Hypertension	5	3	2
	Palpitation	3	6	5
CNS/PNS	Insomnia	39	30	24
	Dizziness	22	23	10
	Paresthesia	13	10	9
	Amnesia	10	9	2
	Hypesthesia	10	8	8
	Hypertonia	7	10	6
	Confusion	4	6	4
	Somnolence	4	8	5
ENDOCHINE DISORDERS	Thyroid Test Abnormal	9	5	4
FLU-LIKE SYMPTOMS§	Headache	82	83	78
	Fatigue	69	67	66
	Fever	61	45	58
	Myalgia	58	56	51
	Rigors	57	45	62
	Arthralgia	51	45	43
	Sweating Increased	12	11	13
GASTRO-INTESTINAL	Abdominal Pain	41	40	34
	Nausea	40	36	39
	Diarrhea	29	24	24
	Anorexia	24	17	21
	Dyspepsia	21	16	12
	Vomiting	12	11	15
	Constipation	9	5	5
	Flatulence	8	9	6
	Tooth Ache	7	7	3
	Hemorrhoids	6	3	1
	Saliva Decreased	6	7	4
HEARING-VESTIBULAR	Tinnitus	6	4	4
	Earache	5	3	5
	Otitis	2	5	1

(Continued)

Table 2. Patient Incidence of Adverse Events in Phase 3 Clinical Trials Regardless of Attribution* (Continued)

		Initial Treatment†		Subsequent Treatment‡
		Infergen 9 mcg (n = 231)	IFN α-2b 3 Million IU (n = 236)	Infergen 15 mcg (n = 165)
Body System	Preferred Term	Percentage of Patients		Percentage of Patients
HEMATOLOGIC	Granulocytopenia	24	25	42
	Thrombocytopenia	19	16	18
	Leukopenia	15	13	19
	Ecchymosis	6	8	4
	Lymphadenopathy	6	8	4
	Lymphocytosis	5	3	11
	PT Increased	3	5	1
LIVER AND BILIARY	Liver Tender	5	3	5
	Hepatomegaly	3	5	5
METABOLIC-NUTRITION	Hypertriglyceridemia	6	7	5
MUSCULO-SKELETAL	Back Pain	42	37	29
	Limb Pain	26	25	13
	Neck Pain	14	13	8
	Skeletal Pain	14	14	10
	Musculo-skeletal Disorder	4	4	7
PSYCHIATRIC DISORDER	Nervousness	31	29	16
	Depression	26	25	18
	Anxiety	19	16	10
	Emotional Lability	12	11	6
	Thinking Abnormal	8	12	10
	Agitation	6	6	4
	Libido Decreased	5	5	5
REPRODUCTIVE-FEMALE	Dysmenorrhea	9	9	2
	Vaginitis	8	2	5
	Menstrual Disorder	6	5	2
	Moniliasis Genital	2	6	2
	Pain Breast	0	5	2
RESISTANCE MECHANISM	Infection	3	5	2
RESPIRATORY	Pharyngitis	34	31	17
	Infection Upper Respiratory	31	34	16
	Cough	22	17	12
	Sinusitis	17	22	12
	Rhinitis	13	16	7
	Respiratory Tract Congestion	12	7	5
	Upper Respiratory Tract Congestion	10	14	7
	Epistaxis	9	12	6
	Dyspnea	7	12	8
	Bronchitis	6	6	2
SKIN AND APPENDAGES	Alopecia	14	25	10
	Pruritus	14	14	11
	Rash	13	15	13
	Erythema	6	6	6
	Skin Dry	6	5	2
	Wound	4	7	3
SPECIAL SENSES	Taste Perversion	3	6	3
VISION DISORDERS	Conjunctivitis	8	8	4
	Eye Pain	5	6	4
	Vision Abnormal	3	5	5

* Only events that occurred at a frequency of ≥ 5% in any treatment group are included. Patients can appear more than once in Table 2. Because the two studies were conducted at different times with nonidentical patient groups, the adverse events profile for the sub-sequent treatment study is not directly comparable to the initial treatment study.

† Adverse events reported in patients during treatment or post-treatment observation in the pivotal initial treatment and subsequent treatment studies are listed regardless of attribution to treatment.

‡ Influenza-like symptoms: Presumed viral etiology.

Laboratory Values

The following laboratory variables were found to be affected by therapy with Infergen in the 231 patients who received treatment with 9 mcg Infergen.

Hemoglobin and Hematocrit: Treatment with Infergen was associated with gradual decreases in mean values for hemoglobin and hematocrit, which were 4% and 5% below baseline at the end of treatment. Decreases from baseline of 20% or more in hemoglobin or hematocrit were seen in 1% of patients or less.

White Blood Cells: Infergen treatment was associated with decreases in mean values for both total white blood cell (WBC) count and ANC within the first 2 weeks of treatment. By the end of treatment, mean decreases from baseline of 19% for WBCs and 23% for ANC were observed. These effects reversed during the post-treatment observation period. In two Infergen-treated patients in the phase 3 trial, decreases

in ANC to levels below 500 x 10^6 cells/L were seen. In both cases, the ANC returned to clinically acceptable levels with reduction of the dose of Infergen, and these transient decreases in neutrophils were not associated with infections.

Platelets: Infergen treatment was associated with alterations in platelet count. Decreases in mean platelet count of 16% compared to baseline were seen by the end of treatment. These decreases were reversed during the post-treatment observation period. Values below normal were common during treatment with 3% of patients developing values less than 50 x 10^6 cells/L, usually necessitating dose reduction.

Triglycerides: Mean values for serum triglyceride increased shortly after the start of administration of Infergen, with increases of 41% compared with baseline, at the end of the treatment period. Seven percent of the patients developed values which were at least three times above pretreatment levels during treatment. This effect was promptly reversed after discontinuation of treatment.

Thyroid Function: Infergen treatment was associated with biochemical changes consistent with hypothyroidism including increases in TSH and decreases in T_4 mean values. Increases in TSH to greater than 7 mU/L were seen in 10% of 9 mcg Infergen-treated patients either during the treatment period or the 24-week post-treatment observation period. Thyroid supplements were instituted in approximately one third of these patients.

Laboratory Values for Subsequent Treatments: From a database of 165 patients receiving treatment with 15 mcg of Infergen after failing initial interferon therapy, similar changes in the laboratory variables as outlined above were observed. However, mean decreases from baseline of 23% for WBCs and 27% for ANC were observed, which was greater than during initial treatment. Reductions in WBCs and ANC resulted in alteration of doses in 11 patients (7%). Two patients experienced reversible reductions in ANC to < 500 x 10^6 cells/L, which were not associated with infectious complications. No patients discontinued as a result of hematologic toxicity.

OVERDOSAGE

In Infergen trials, the maximum overdose reported was a dose of 150 mcg Infergen administered SC in a patient enrolled in a phase 1 advanced malignancy trial. The patient received 10 times the prescribed dosage for 3 days. The patient experienced a mild increase in anorexia, chills, fever, and myalgia. Increases in ALT (15 to 127 IU/L), aspartate transaminase (AST) (15 to 164 IU/L), and lactic dehydrogenase (LDH) (183 to 281 IU/L) were reported. These laboratory values returned to normal or to the patient's baseline values within 30 days.

DOSAGE AND ADMINISTRATION

The recommended dose of Infergen for treatment of chronic HCV infection is 9 mcg TIW administered SC as a single injection for 24 weeks. At least 48 hours should elapse between doses of Infergen. Should a patient miss a scheduled dose, the missed dose should be taken as soon as possible, and the administration schedule revised at the physician's discretion.

Patients who tolerated previous interferon therapy and did not respond or relapsed following its discontinuation may be subsequently treated with 15 mcg of Infergen TIW for 6 months. Patients should not be treated with 15 mcg of Infergen TIW if they have not received, or have not tolerated, an initial course of interferon therapy.

There are significant differences in specific activities among interferons. Health care providers should be aware that changes in interferon brand may require adjustments of dosage and/or change in route of administration. Patients should be warned not to change brands of interferon without medical consultation. Patients should also be instructed by their physician not to reduce the dosage of Infergen prior to medical consultation.

Dose Reduction

For patients who experience a severe adverse reaction on Infergen, dosage should be withheld temporarily. If the adverse reaction does not become tolerable, therapy should be discontinued. Dose reduction to 7.5 mcg may be necessary following an intolerable adverse event. In the pivotal study, 11% of patients (26/231) who initially received

Infergen at a dose of 9 mcg (0.5 mL) were dose-reduced to 7.5 mcg (0.25 mL).

If adverse reactions continue to occur at the reduced dosage, the physician may discontinue treatment or reduce dosage further. However, decreased efficacy may result from continued treatment at dosages below 7.5 mcg.

During subsequent treatment with 15 mcg of Infergen, 33% of patients required dose reductions in 3 mcg increments.

Administration of Infergen

If home use is determined to be desirable by the physician, instructions on appropriate use should be given by a health care professional. After administration of Infergen, it is essential to follow the procedure for proper disposal of syringes and needles. See "Information For Patients" leaflet for detailed instructions provided separately.

Storage

Infergen should be stored in the refrigerator at 2° to 8°C (36° to 46°F). Do not freeze. Avoid vigorous shaking and exposure to direct sunlight. Just prior to injection, Infergen may be allowed to reach room temperature.

Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, if particulates or discoloration are observed, the container should not be used.

HOW SUPPLIED

Use only one dose per vial; do not re-enter the vial. Discard unused portions. Do not save unused drug for later administration.

Use only one dose per prefilled syringe. Discard unused portions. Do not save unused drug for later administration.

Vials

Single-dose, preservative-free vials containing 9 mcg (0.3 mL) of Interferon alfacon-1 are available in dispensing packs of six vials (NDC 55513-554-06).

Single-dose, preservative-free vials containing 15 mcg (0.5 mL) of Interferon alfacon-1 are available in dispensing packs of six vials (NDC 55513-562-06).

Prefilled Syringes (Singleject™)

Single-dose, preservative-free prefilled syringes containing 9 mcg (0.3 mL) of Interferon alfacon-1 are available in dispensing packs of six prefilled syringes (NDC 55513-926-06).

Single-dose, preservative-free prefilled syringes containing 15 mcg (0.5 mL) of Interferon alfacon-1 are available in dispensing packs of six prefilled syringes (NDC 55513-927-06).

Infergen should be stored at 2° to 8°C (36° to 46°F). Do not freeze. Avoid vigorous shaking.

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AMGEN®

Manufactured by:
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3181500
Issue Date: 11/30/98